

REMARKS

I. Claim Status

By this Amendment, claim 1 is amended to more clearly define the claimed subject matter and claims 2-4 and 7-16 are canceled without prejudice or disclaimer. Upon entry of this Amendment, claims 1, 6, and 17-19 will be pending. Support for the amendments is present in the specification as filed at least at, e.g., p. 8, ll. 10-15; p. 8, ll. 32-36; p. 9, ll. 6-11; p. 18, ll. 25-36; and in the original claims. No new matter is added.

II. 35 U.S.C. § 103 (a)

Claims 1, 4, 6, and 13-19 have been rejected as allegedly obvious over Schiffmann et al., *Proc. Natl. Acad. Sci. U.S.A.* 97:365-370 (2000) or Desnick et al., *Proc. Natl. Acad. Sci. U.S.A.* 76:5326-5330 (1979), each in view of Ziegler et al. *Hum. Gene Ther.* 10:1667-1682 (1999) and Intl. Pat. Appl. Pub. No. WO 98/11206.

The *prima facie* case of obviousness based on the above references is no longer relevant in view of amendments to the claims, as none of the cited references teaches or suggests administration of enzyme replacement therapy *subsequent* to gene therapy. Therefore, the burden rests with the Examiner to make a proper *prima facie* case for the amended claims. Applicants further submit that the claimed invention is unobvious at least because of the unexpected results discussed below.

Treatment of a subject with enzyme replacement therapy is known to produce deleterious immune responses in that subject, whereby the subject's body raises an immune response to the administered enzyme. Specification, p. 19, ll. 18-19. Such an

immune response neutralizes the replacement enzyme, reducing the efficacy of the enzyme replacement therapy. However, the Applicants have found that treatment of Fabry mice by gene therapy results in the unexpected development of immune tolerance towards the expressed α -galactosidase A. A report of these findings was published by Ziegler et al., *Mol. Ther.* 9:231-230 (2004) at, e.g., p. 233, col. 2, l. 1 to p. 234, col. 1, l. 3; p. 234, col. 2, l. 1 to p. 235, col. 1, l. 2; p. 235, col. 1, l. 24 to p. 235, col. 2, l. 5; and Figures 5A and 6. This finding has been additionally demonstrated in a murine model of Niemann-Pick disease and reported in Barbon et al., *Mol. Ther.* 12:431-440 (2004) (see, e.g., p. 436, col. 2, ll. 6-22). (Copies of these articles are provided with the Information Disclosure Statement filed with this submission.) It is believed, but not relied upon for the purposes of the invention, that the immune tolerance results from the gradual, low-level expression of the protein encoded by the gene introduced through gene therapy. Based on these findings, it is expected that a human subject having Fabry disease will likewise develop immune tolerance towards α -galactosidase A upon gene therapy with a viral or non-viral vector encoding α -galactosidase A.

According to the methods of the invention as presently claimed, a subject is first treated with gene therapy and then subsequently treated with enzyme replacement therapy. Such a combination was not taught or suggested in the cited prior art, and is inventive. In particular, the data discussed above demonstrate that this mode of combination therapy has unexpected advantages that were not present in the prior art. Specifically, upon treatment by enzyme replacement therapy, the tolerized subject would have higher overall levels of the administered α -galactosidase A than a control

subject not previously treated with gene therapy. This allows for higher efficacy of treatment in the tolerized subject. For example, it may be possible to treat the tolerized subject with lower doses of replacement enzyme, or to administer replacement enzyme less frequently than would otherwise be possible. Thus, pre-treatment with gene therapy according to the methods of the claimed invention provides significant advantages over the prior art.

In conclusion, the methods of the claimed invention do not possess an expected property, i.e., practice of the claimed method does not result in the expected immune response to a replacement enzyme. This absence of an expected property is an unexpected result sufficient to establish unobviousness within the meaning of 35 U.S.C. § 103 (a). M.P.E.P. § 716.02, *esp.* § 716.02 (a) IV.


Therefore, Applicants respectfully request a speedy allowance of claims. Should the Examiner have any questions, the Examiner is welcome to call the undersigned applicants' representative at the number below.

Please grant any extensions of time required to enter this response and charge any additional required fees to deposit account 06-0916.

Respectfully submitted,

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Dated: February 10, 2006

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